REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 8-9 have been canceled, the dependency of claim 10 has been amended, and claim 32 is added. Therefore, claims 1-4, 6-7, and 10-32 are currently pending.

Support for new claim 32 is found in the specification as originally filed, such as in original claims 8 and 9.

Claims Rejections under 35 U.S.C. §112, first paragraph (Written Description)

Claims 1-4 and 6-31 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner states that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 8-9 have been canceled, and claim 32 has been added. Insofar as this rejection is applied to the pending claims, it is hereby traversed.

Claim 1 recites a somatic cell gene targeting vector comprising a gene targeting construct comprising a first cloning site operably linked to a DNA encoding a positive selection marker, a second cloning site and a first polyadenylation sequence, wherein the construct is promoterless, wherein the first cloning site comprises a first DNA segment that is homologous to a first genomic target sequence and the second cloning site comprises a second DNA segment that is homologous to a second genomic target sequence; and an expression cassette comprising a promoter operably linked to DNA encoding a negative selection marker and a second polyadenylation sequence. Claim 32 is similar to claim 1, adding the feature that the promoter is a weak promoter, a phosphoglycerate kinase (PGK) promoter or a modified Rous sarcoma virus (RSV) promoter. Claims 2-4, 6-7, 10-12, 30-31 depend either directly or indirectly from claims 1 or 32. It should be noted that claims 1-4, 6-12, and 30-31 are composition claims and not method claims, and therefore, do not recite disrupting a gene of interest.

Claims 13 and 20 recite methods for disruption of a gene of interest in a somatic cell using a gene targeting construct. Claims 14-19, and 28 depend either directly or indirectly from claim 13, and claims 22-27 and 29 depend either directly or indirectly from claim 20. These

claims recite methods of disrupting a gene of interest in a somatic cell *in vitro*, such as to study the function of gene or to create cell lines.

The examiner states that the claimed vector and method of disrupting genes of interest are so broad as to encompass a somatic cell gene targeting vector for any gene of interest and a method of use of that vector to target any gene of interest. Specifically, the examiner stated at page 4 of the Office Action that "in order to disrupt known Gene X, the sequence of Gene X, including locations of exons and introns would be required." Determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by those skilled in the art. Applicant asserts that at the time the application was filed, sequences (including intron and exon structure) for the vast majority of genes of many organisms were, in fact, available to the inventors and other scientists. Such information was readily available for almost all genes of interest, and was easily accessible by multiple databases that were completely in the public domain. Both the human and mouse genomes have been completely sequenced, in addition to complete genomes (or at least large amounts of genomes) of other organisms that are of interest to scientists. Thus, the statement that "neither the skilled artisan nor the inventors have possession of the genomic structure of the enormous number of genes of interest" is inaccurate.

Page 5 of the Office Action states that citation of the Wang et al. and Norgren review articles was "meant to emphasize that the specification does not provide sufficient descriptive support for the complete genus of claimed gene targeting vector for the claimed function of disrupting any gene of interest, since the claimed function is complex" and that "Wang et al teach that gene targeting in somatic cells is 'more difficult' that in mouse ES cells." Claims 1-4, 6-12, or 30-31 are composition claims and therefore do not recite function (*i.e.*, the disruption of a gene of interest). Insofar as this rejection is applied to the pending method claims, it is hereby traversed. Applicant would like to point out that the claimed vector specifically contains features that address that fact that gene targeting is "more difficult" in somatic cells than mouse ES cells. This was, in fact, a primary motivating factor for producing this vector. All the features of the claimed vector described as different from ES targeting vectors in the application were designed to overcome this challenge, and have done so.

Applicant asserts that the specification provides adequate written description for the claimed invention. The relevant art area was mature at the time the application was filed, and many genes, and even whole genomes, were known by those of skill in the art at the time the application was filed. Once the inventors instructed the person of skill what pieces needed to go into the construct, one of skill in the art would know the molecular biology necessary to make a construct. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph (written description) be withdrawn.

Claims Rejections under 35 U.S.C. §103(a)

Claims 1-4, 6-7 and 11-12 are rejected under 35 U.S.C. §103(a) as being unpatenable over Capecchi et al. (U.S. Patent No. 5,631,153) in view of Sedivy et al. (Trends in Gen. 15:88-90 (1999)). As discussed above, claim 1 recites a somatic cell gene targeting vector comprising a gene targeting construct comprising a first cloning site operably linked to a DNA encoding a positive selection marker, a second cloning site and a first polyadenylation sequence, wherein the construct is promoterless, wherein the first cloning site comprises a first DNA segment that is homologous to a first genomic target sequence and the second cloning site comprises a second DNA segment that is homologous to a second genomic target sequence; and an expression cassette comprising a promoter operably linked to DNA encoding a negative selection marker and a second polyadenylation sequence. Claims 2-4, 6-7, and 11-12 depend either directly or indirectly from claim 1.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. MPEP Section 706.02(j).

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination.

In re Napier, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995). The mere fact that the prior art could be so modified would not have made the modification obviousness the prior art suggested the desirability of the modification. *In re Laskowski*, 871 F.2d 115, 117, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989). There must be a reason or suggestion in the art for selecting the pieces used, other than the knowledge learned from the applicant's disclosure. Using an applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art contravenes the statutory mandate of Section 103 which requires judging obviousness at the point in time when the invention was made. *Grain Processing Corp. v. American Maize-Prods. Co.* 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988). An Examiner must not merely cite reference showing that the claimed elements or sub-combinations of them were known. Most inventions arise from a combination of old elements and each element may often be found in the prior art. *In re Kahn,* 441 F.3d 977, 986 (Fed. Cir. 2006). However, mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. *Id.*

Applicant asserts that the examiner has not shown a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention.

Capecchi et al. disclose positive-negative selector (PNS) vectors for modifying a target DNA sequence contained in the genome of a target cell capable of homologous recombination. The vectors comprise a first DNA sequence substantially homologous a first region of a target DNA sequence, a second DNA sequence substantially homologous to a second region of a target DNA sequence, a third DNA sequence positioned between the first and second DNA sequences that encodes a positive selection marker (which can be a promoterless positive selection marker), and a fourth DNA sequence encoding a negative selection marker.

Capecchi et al. do not disclose polyadenylation sequences operably linked to the positive selection marker, as recited by claim 1. Capecchi et al. list a number of "regulatory sequences" that can be used to control expression of the negative and/or positive selection markers (Table IIB), and states that the "regulatory sequences" are, e.g., "enhancers and promoters" (col. 13,

lines 65-67). A "regulatory sequence" (also called regulatory region or ~ element) is defined as "a promoter, enhancer or other segment of DNA where regulatory proteins such as transcription factors bind preferentially. They control gene expression and thus protein expression." (Wikipedia, August 3, 2006, copy of definition attached hereto). Polyadenylation sequences are not "regulatory sequences" as this term is used by Capecchi et al. Therefore, even if Sedivy were to teach the use of a polyadenylation sequence, there is no teaching or suggestion in Capecchi et al. to insert a polyadenylation sequence into the gene targeting cassette, because Capecchi et al. teach that various "regulatory sequences" can be interchanged, but do not teach that polyadenylation sequences can be added to the gene targeting cassette. Thus, there is no motivation to pick one element (a polyadenylation sequence) out of Sedivy and insert it into the construct of Capecchi et al. Sedivy does not teach a promoterless PNS vector, and therefore cannot teach the use of a polyadenylation sequence with a promoterless PNS vector, as recited in claim 1.

Further, Capecchi et al. do not disclose excision of the positive selection sequences using site-specific recombination sequences, such as loxP sequences (as recited by claims 2-4). Sedivy suggests that sequential gene targeting can be facilitated by recycling a positively selectable gene by using cre-lox system of site-specific recombination (Sedivy at page 90). Capecchi et al. do not teach or suggest sequential gene targeting, so that one of skill in the art would not have been motivated to modify the construct of Capecchi et al. by inserting the cre-lox PNS cassette of Sedivy into their construct. Moreover, even if one were motivated to modify the Capecchi et al. construct by inserting the cre/lox PNS cassette of Sedivy, one would have added a positive-negative selection cassette that includes both a promoter-driven neo resistance gene as well as a thymidine kinase gene, because that is what Sedivy taught. Sedivy did not teach the combination of a promoterless positive selection marker in combination with a cre/lox system.

Sedivy discloses PNS vectors where the positively and negatively selectable genes are functionally independent expression cassettes, and each contains its own promoter and polyadenylation signals (p. 88, second column and Fig. 1). Sedivy also discloses promoterless vectors, and PNS vectors, but not promoterless PNS vectors. Applicant asserts that one of skill in the art would not have modified Sedivy to use a promoterless PNS vector, considering Sedivy himself was aware of PNS vectors and promoterless vectors (see Figure 1), and yet did not teach

or suggest a promoterless PNS vector. The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention, and there is no motivation in Sedivy to modify the constructs disclosed therein to generate a promoterless PNS vector.

Thus, there is no motivation, desirability or incentive in the art to modify the art to make the modification needed to arrive at the claimed invention. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby. If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

Gail Bishop et al.

By their Representatives,

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